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An efficient stochastic diffusion algorithm for modeling second messengers in dendrites and spines

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Abstract

Intracellular signaling pathways, which encompass both biochemical reactions and second messenger diffusion, interact non-linearly with neuronal membrane properties in their role as essential intermediaries for synaptic plasticity and neuromodulation. Computational modeling is a productive approach for investigating these phenomena; however, most current strategies for modeling neurons exclude signaling pathways. To overcome this deficiency, a new algorithm is presented to simulate stochastic diffusion in a highly efficient manner. The gain in speed is obtained by considering collections of molecules, instead of tracking the movement of individual molecules. The probability of a molecule leaving a spatially discrete compartment is used to create a lookup table that stores the probability of k_m molecules leaving the compartment as a function of the total number of molecules in the compartment. During the simulation, the number of molecules leaving the compartment is determined using a uniform random number as an index into the lookup table. Simulations illustrate the accuracy of this algorithm by comparing it with the theoretical solution for deterministic diffusion. Additional simulations show how spines on a dendritic branch compartmentalize diffusible molecules. The efficiency of the algorithm is sufficient to allow simulation of second messenger pathways in a multitude of spines on an entire neuron.

Keywords: Diffusion; Stochastic; Second messenger; Computer software

1. Introduction

Intracellular signaling pathways, which encompass both biochemical reactions and second messenger diffusion, are critically intertwined with neuronal function, as has been documented in several brain areas. In the hippocampus, AMPA receptors are modulated by several kinases and phosphatases (Malinow et al., 1989; Malenka et al., 1989; Tsien et al., 1996; Abel et al., 1997) which themselves are activated by calcium influx through NMDA receptors and voltage-dependent channels. In the striatum, several membrane channels are modulated by DARPP-32 signaling pathways (Surmeier et al., 1995), which activation depends on neuronal activity. These non-linear and feedback interactions make it exceedingly difficult to understand how neuronal activity is modulated by spatio-temporal input patterns that occur in vivo.

Computational modeling is an innovative, yet practical method to investigate neuronal function. On the macroscopic scale, modeling has made significant contributions regarding the influence of morphology and channel properties on neuronal integration (e.g. Poirazi et al., 2003a, 2003b; Migliore et al., 2004). On the microscopic scale, computational models of cellular signaling pathways have been employed to understand neurotransmitter release and generation of miniature endplate currents (e.g. Stiles et al., 1999), as well as kinase activation in spines (e.g. Bhalla, 2004a, 2004b). However, due to computational complexity, most current strategies for modeling neurons exclude either complex molecular interactions or electrical membrane properties that underlie synaptic modulation. The few neuron models that do include reaction–diffusion subsystems employ continuous, deterministic equations (e.g. Blackwell, 2004; Fink et al., 2000), which assume large numbers of molecules in each compartment.

An intermediate approach, on the mesoscopic scale, is required to adequately model the interaction between cell signaling pathways and neuronal activity. The biochemical reactions leading to activation of kinases and phosphatases are localized to dendritic spines (Rosenmund et al., 1994; Westphal et al., 1998); thus these small structures must be included in whole neuron models. A stochastic approach is required to adequately

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describe bimolecular interactions among the small numbers of molecules within the spine (Gillespie, 1977) because activations fluctuate greatly about the mean within such small compartments. Similarly, diffusion of second messenger molecules out of the spines and along the thin dendrites also must be described using stochastic equations. Thus, an effective model of synaptic modulation requires the fusion of the complexities of neuronal membrane physiology with highly efficient models of molecular interactions.

Though highly efficient algorithms for stochastic bimolecular reactions are available (e.g. Gibson and Bruck, 2000; Cao et al., 2005), algorithms for stochastic diffusion are less numerous. The simplest diffusion algorithms employ random walk with discretized space and time. The disadvantage is that increased accuracy requires finer (and thus computationally slower) time discretization. To integrate with biochemical reactions, only those molecules in the same spatial location are considered for interactions. Another discrete space approach for reaction–diffusion systems is to consider diffusion as an additional reaction. The appropriate reaction coefficient (diffusion propensity) is calculated from the diffusion coefficient and the geometry (compartment size). Two algorithms employ this approach (Elf et al., 2003; Bhalla, 2004a), but these algorithms consider individual molecules, and thus may not scale well for neurons. An alternative and more efficient approach is to avoid spatial discretization and to use ray tracing to evaluate when diffusers interact (e.g. Stiles and Bartol, 2001; Tuerlinckx et al., 2001). Though the Monte Carlo algorithm employed by MCell is the most computationally efficient method for creating exact stochastic simulations of diffusion and reactions, reactions are not allowed among two diffusing species. Further gains in speed are required for modeling diffusion and reactions in entire neurons.

The algorithm presented below is an accelerated approximation to stochastic diffusion. Though a spatial discretization is employed, the gain in speed is obtained by considering collections of molecules, instead of tracking the movement of individual molecules. The efficiency of the algorithm is sufficient to allow simulation of second messenger pathways in a multitude of spines on the dendritic trees of an entire neuron.

2. Methods

Consider a structure, such as a spine subdivided into spatial compartments of length Δx. The probability that a molecule will leave the spatial compartment is proportional to the time step, ΔT, multiplied by the diffusion coefficient, D, divided by the length of the compartment, Δx (Elf et al., 2003; Bhalla, 2004a):

$$P_{\mathrm{m}} = 2D\,\frac{\Delta T}{\Delta x^2} \tag{1}$$

Of the molecules that leave the compartment, half will move forward, and half will move backward; the remaining molecules in the compartment will not leave the compartment. The computational efficiency arises from the recognition that, given these three probabilities: moving forward ($p_{\mathrm{f}} = P_{\mathrm{m}}/2$), moving backward ($p_{\mathrm{b}} = P_{\mathrm{m}}/2$) or not moving ($p_{\mathrm{n}} = 1 - P_{\mathrm{m}}$), the number of molecules moving forward (k_{f}), backward (k_{b}), or not leaving ($N - k_{\mathrm{f}} - k_{\mathrm{b}}$) in a compartment can be calculated with the trinomial distribution:

$$P(N, k_{\mathrm{f}}, k_{\mathrm{b}}) = \frac{N!}{k_{\mathrm{f}}!k_{\mathrm{b}}!(N - k_{\mathrm{f}} - k_{\mathrm{b}})!}\, p_{\mathrm{f}}^{k_{\mathrm{f}}} p_{\mathrm{b}}^{k_{\mathrm{b}}} p_{\mathrm{n}}^{(N-k_{\mathrm{f}}-k_{\mathrm{b}})} \tag{2}$$

Thus, if a compartment contains 20 molecules, instead of choosing 20 random numbers, it is only necessary to choose a single random number to determine the destination of each molecule within a compartment. Though trinomial random numbers are expensive to generate, the use of a pre-defined lookup table, which stores cumulative probabilities as a function of N, k_{f} and k_{b}, allows the algorithm to use uniform random numbers.

Two minor differences are required to apply the algorithm to diffusion in two or three dimensions. First, the probability of leaving the compartment, p_{m}, must account for additional spatial dimensions, e.g. in two dimensions:

$$p_{\mathrm{m}} = \frac{2D\Delta T}{\Delta x^2} + \frac{2D\Delta T}{\Delta y^2} + \frac{(2D\Delta T)^2}{\Delta x^2 \Delta y^2} \tag{3}$$

where Δx and Δy are the sizes of the two-dimensional compartment. Second, the number of particles moving, k_{m}, is calculated from the binomial:

$$P(N, k_{\mathrm{m}}) = \frac{N!}{(N - k_{\mathrm{m}})!k_{\mathrm{m}}!}\, p_{\mathrm{m}}^{k_{\mathrm{m}}}(1 - p_{\mathrm{m}})^{(N-k_{\mathrm{m}})} \tag{4}$$

Similar to the one-dimensional algorithm, a pre-defined lookup table that stores cumulative binomial probabilities allows k_{m} to be determined with a single uniform random number. Specifically, given the random number u and total number of molecules N, a binary search of row N in binomial table T_{B} is used to find the binomial probability table entry, $T_{\mathrm{B}}(N, j)$, such that $T_{\mathrm{B}}(N, j-1) < u < T_{\mathrm{B}}(N, j)$. Then the number of moving molecules is read out from a parallel lookup table, T_{K} that stores the corresponding number of moving molecules, using row N and index j: $k_{\mathrm{m}} = T_{\mathrm{K}}(N, j)$. After the number of moving molecules is calculated, the destination compartment of each molecule is determined in a similar manner using a uniform random number as index to a table which stores the probability of moving in each compartment direction.

The algorithm is illustrated in Fig. 1. A flow chart of the initialization steps is portrayed in Fig. 1A. First, the geometry of the structure is defined. For a neuron, each segment of the dendritic tree is subdivided into equal size compartments. Second, the connectivity of the compartments is stored in an array. From the compartment size, diffusion coefficient, and time step, the probability is calculated of a molecule moving from one compartment to any adjacent compartment. Third, the binomial distribution (or trinomial distribution where 1D is appropriate) is used to create the table of probabilities that k_{m} out of N molecules leaves the compartment, for N between 1 and $N_{\max}$. Lastly, a second table is created which enumerates the probabilities of moving in each direction (i.e. North, South, Northeast, etc). In circumstances where the dendrites have spines, a connection array is created to map each spine to a dendritic compartment, and the direction table is modified to include the probability of a molecule moving into a spine.